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Article (Accepted Version)

Extended release delivery system of metoprolol succinate using hot melt extrusion: effect of release modifier on methacyrlic acid copolymer

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Abstract:

The current study reports on the manufacturing of extended release dosage forms of Metoprolol succinate via hot-melt extrusion (HME) technology. Either Eudragit®S100 and Eudragit®L100 alone or in combination with release modifying agent Polyox™ WSR 303 and Eudragit®L100-55 were processed to obtain complete and faster release. Metoprolol Succinate with similar solubility parameters to polymer were dispersed in polymer matrix, and was characterized by Fourier Transform Infra-red Spectroscopy (FT-IR), differential scanning calorimetry (DSC), X-ray diffraction (XRD) and Scanning electron microscopy (SEM). Stability of drug after extrusion was confirmed by thermogravimetric analysis and high performance liquid chromatography. Physical characterization method exhibited that the drug was homogeneously dispersed in non-crystalline state in Eudragit®L100-55 based formulations whereas in semi-crystalline state in Polyox™ WSR 303. The drug release percentage was below 3% and 40% in 0.1N HCL with Eudragit®L100-55 and Polyox™ WSR 303 containing formulations, respectively and exhibited pH dependent dissolution properties. The drug release mechanism was anomalous with Polyox™ WSR 303 formulations whereas diffusion through pore formation was obtained with Eudragit®L100-55. Both Eudragit®L100-55 and Polyox™ WSR 303 changed the release mechanism and kinetics of drug release from thermally processed dosage forms. The optimized stable formulation is similar to the marketed formulation with F2 value is 72.36. Thus, it can be concluded that HME was exploited as an effective process for the preparation of controlled release matrix system based on pH dependent polymer matrices Eudragit®S100 and Eudragit®L100.

Keywords: Hot melt extrusion, Metoprolol succinate, Eudragit®S100 and Eudragit®L100 Eudragit®L100-55, Polyox™ WSR 303, extended release, release modifying agent

Abbreviations: Hot Melt Extrusion [HME], Metoprolol Succinate [MSN], Eudragit® S100 [S100], Eudragit® L100 [L100], Polyox™ WSR 303 [PEO303], Eudragit® L100-55 [L100-55]

1. Introduction:

Solid dispersion- a mixture of two compounds that are generally solid in room temperature, of drug candidates has appeared as a well-known technique for the enhancement of solubility and controlling release of drug candidates from many decades [1]. Pharmaceutical HME has been adopted as a continuous processing technology of converting drug–polymer mixture blend into a product of uniform shape with desired properties. The extrudates evacuate via a die under pre-optimized temperature, speed, feeding rate and pressure conditions. Appropriate selection of die offers possibilities to formulate variety of solid dosage forms such as granules, pellets, tablets, suppositories, implants, stents, transdermal and transmucosal systems, and ophthalmic inserts. [2-5]. The advantage of using HME includes no use of solvents (lowers hazards), automation of the production process, high throughput, reduced material loss and high yields matrices with excellent homogeneity (few processing steps and reduced cost) [6-7]. During the HME process, heated polymer function as thermal binder and acts as drug depots or drug release retardants upon cooling and solidification [1]. This results in formation of compact mass which gives sustained release property with minimum quantity of polymer. Use of ethylcellulose [8-9], ethylene-vinyl acetate [10], hyper branched polymer Hybrane H1500 [11], Kollidon® SR [12], hydroxypropyl Cellulose [13], Polyethylene Oxide [14], Acryl-EZE® [15] were reported to have showed a sustained release of various maodel drugs processed via HME and thus are well-used as sustained release polymers for pharmaceutical HME applications.

Metoprolol succinate (MSN) is a selective beta-adrenergic receptor blocker useful in treatment of hypertension, angina and heart failure. MSN has a high aqueous solubility and high permeability (BCS class-I) throughout gastrointestinal tract [16]. The plasma half-life ranges from approximately 3 to 7 hours. A pharmacodynamics study conducted by G. JOBIN' and coworkers showed Metoprolol was not absorbed from the stomach and absorbed throughout the intestinal tract [17-19].

Hydrophilic matrix system is the most common method to prepare extended release formulations. This requires 5 to 6 times polymer concentration to obtain desired release. Also, many steps are involved for sustained release tablet formulation. Based on the above observation, a single step HME technology was employed to prepare extended release tablets of MSN with minimum quantity of Eudragit S100 and Eudragit L100 polymer in order to control

the release of the hydrophilic drug. In order to increase the permeability through melt extruded S100 and L100 matrix, two release modifier polymers Polyox^{TM} WSR 303 and Eudragit L100-55 were used based on their thermal and permeation enhancing properties. The optimized formulation was evaluated for in-vitro release using commercial Actiblock IPR100 and Betaone XL100 with 100mg MSN.

2. Materials and Methods:

2.1 Materials

MSN (99.9% purity) was kindly gifted by CTX Life Sciences Private Limited Mumbai. Eudragit grades L100, S100 and L100-55 were kindly donated by Evonik, Germany. PEO 303 was gifted from Dow Chemicals, USA. Acetonitrile (HPLC), sodium lauryl sulphate and ortho phosphoric acid were bought from SD-fine chemicals, Mumbai, India. Actiblok IPR 100 from Biocon and Betaone XL100 from Dr. Reddy's Lab containing 100 mg metoprolol succinate were purchased.

2.2 Methods:

2.2.1 Thermogravimetric analysis

A TGA-DSC was employed to investigate thermal stability of MSN and polymer. This was analyzed by Thermogravimetric analysis SDT Q600 v8.2 Build 100 model of TA instruments. Measurements were performed with 5 mg of sample placed in platinum crucibles. Samples were maintained at 40°C for 1 min and then heated to 600°C at a heating rate of 10°C/min under nitrogen atmosphere (50 $mlmin^{-1}$). For the dynamic stability studies, samples were held at 160°C for 15 min and the percentage weight loss was measured. Dynamic thermal stability studies were carried out and the mass change of the samples as a function of time in the isothermal mode was measured. The thermal data obtained was processed usingTA60 software. Thermal stability of prepared extrudates was performed.

2.2.2 Calculation of Solubility parameters (δ) and glass transition temperature (Tg)

The solubility parameter of drug and polymer were calculated by group contribution method using Hoftyzer and van Krevelen method [20] described by the following equation.

$$\sqrt{\delta^2} = \sqrt{\delta^2}_d + \sqrt{\delta^2}_p + \sqrt{\delta^2}_h \qquad (1)$$

where,

$$\delta_d = \sum F_{di}/V,\ \delta_p = \left(\sum F_{pi}^2\right)^{1/2}/V,\ \delta_h = \left(\sum E_{hi}/V\right)^{1/2} \quad \text{.....} \quad \text{a}$$

Here i is the structural groups within the molecule, d is the total solubility parameter, dd is the contribution from dispersion forces, dp is the contribution from polar interactions, dH is the contribution of hydrogen bonding, Fdi is the molar attraction constant due to molar dispersion forces, Fpi is the molar attraction constant due to molar polarization forces, Ehi is the hydrogen bonding energy and V is the molar volume. The solubility parameters of polymer and surfactant combinations were calculated using the following Eq.

$$\delta_{1,2} = Vf_1\delta_1 + Vf_2\delta\rho_2 \quad \text{.....} \quad \text{b}$$

The glass transition temperature of polymer combinations was calculated using the Gordon-Taylor equation (2) [21].

$$Tg_{mix} = (w_1Tg_1 + K_1w_2Tg_2) / (w_1 + K_1w_2) \qquad (2)$$

where, Tg is the glass transition temperature, W1 and W2 are the weight fractions of the components, and K is the parameter calculated from the true densities (q) and Tg of the components

The Tg and ρvalues of other four polymers reported in literature [22, 23,24] and were used in the calculation.

2.2.3 Preparation of MSN extrudates

A dry powder blend containing drug-polymer and release modifier with different concentration were blended in a turbula mixer (Kitchen Aid Inc., USA) for 10 minutes. This drug-excipient blend was processed through HME (single screw) with suitable die size to obtain uniform extrudes at optimized extrusion temperature conditions between 140 to 160°C (S. B. Panchal and Company single screw extruder, Mumbai India). The length/diameter ratio of screw was 25:1. The feed rate was kept at 0.5 gm/min. The screw speed was set at 30 rpm for proper mixing (residence time 2 min in barrel). The MSN extrudates were obtained at the opening of the 6mm die. The extrudates were collected after cooling to ambient temperature. The extrudates were cut manually into small uniform pieces cylindrical shape based on the dose of MSN. Directly

compressed tablet with same polymer ratio was compressed using Cadmach, a single punch tablet press (Batch B03 and B04). The hardness was kept at 18 kgf (8.0 kg/cm^2). These tablets were then used for the comparative studies with the formulations prepared by hot melt extrusion respectively.

2.2.5 Drug Content

Pure MSN and milled extrudates samples equivalent to 10 mg of MSN were weighed accurately and transferred to 100 ml volumetric flask. Samples were dissolved in 20 ml methanol and volume was made up to 100 ml with pH 6.8 phosphate buffer. Samples were filtered through 0.45 µm filter. The drug content was determined by using HPLC equipped with C18 (250 × 4.6 mm) 5µm ID column. The method was followed as reported in literature with slight modification [25]. The mobile phase was 0.1 %w/v orthophosphoric acid solution containing 0.13 % SLS: acetonitrile (85:15 v/v) at 0.5 ml/min flow rate. Photodiode array detector was used at 223 nm wavelength to access the concentration of drug. Borwin Chromatography Software version 1.5 was used for the interpretation of data.

2.2.6 Fourier Transfer Infrared (FT-IR) spectroscopy

FT-IR was performed using a NEXUS 470 FTIR spectroscopy (Nicolet, USA) to investigate possible interaction due to melting process. The samples for IR were prepared by mixing individual components with the potassium bromide (KBr). FT-IR analysis was performed on samples and spectra were generated analytically over a range 4000–400 cm^{-1}. The data was analyzed using spectrum version 10.4.2 software.

2.2.7 Differential scanning calorimetry (DSC) analysis

Differential scanning calorimetry (Perkin Elmer, USA) was used to characterize the thermal behavior of the drug and polymer in hot melt extrudates. Ultrahigh purity nitrogen gas was used as purge gas at a flow rate of 20 ml/min. Approximately 5 mg sample was weighed and sealed in aluminum pans. An empty pan was used as reference pan. Indium was used for the calibration of instrument. The rate of heating was 10°C/min from 40°C to 200°C for all studies.

2.2.8 X-ray Diffraction (XRD)

Powder X-ray diffraction profile of formulation was obtained using a Miniflex apparatus (Rigaku, Japan) with CuKα radiation source. Samples were held on quartz frame. Diffraction pattern were obtained at a voltage of 45 kV and at a current of 40 mA. Samples were scanned in a 2 θ range from 5º to 80º with a scanning speed of 2º/min and an intensity of 3000-4000.

2.2.9 Scanning Electron Microscopy (SEM)

The surface characteristics of MSN extrudes were studied by scanning electron microscopy (SEM). Images were taken with Model JEOL 5400 made in Japan operating at 30kV.The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 Torr, acceleration 200) XL 30. All samples were aluminum-coated at room temperature prior to imaging.

2.2.10 In-vitro release study

The dissolution was performed in pH 1.2 followed by in pH 6.8. The dissolution study was performed using USP type II apparatus (Electrolab dissolution apparatus, TDT 08L, Mumbai) with rotation speed of 50 rpm. The dissolution medium was maintained at 37±0.2°C. In the first 2 hours 750 ml of 0.1N HCl was used to simulate the gastric fluid. After 2 hours, the pH of the medium was increased to 6.8 by the addition of 250 mL 0.2 M sodium triphosphate buffer to simulate the intestinal juice. Aliquots were withdrawn at 1, 2, 3, 7, 11, 15, and 23 hours, filtered over a cellulose acetate filter of 0.45 μm. The withdrawn10 ml aliquot was further diluted10 times before analysis. Samples were analyzed using UV spectrophotometer (Shimadzu, Japan) for in vitro assessment of the amount of drug released from extrudates formulation. The absorbance was measured at 223 nm. All experiments were performed in triplicate.

The dissolution test was also performed as per USP/NF method for PEO303 formulations. The method was operated at 50 rpm speed with 500 ml of dissolution medium of pH 1.2 (0.1N HCl). Aliquots of 10 ml were withdrawn from each vessel at predetermined time intervals 1, 4, 8, and 20 hours. The subsequent method was followed as discussed earlier.

2.2.11 Swelling and water uptake study

HME extrudates were accurately weighed (W1) and placed in vessel of USP apparatus II. Extrudates were added in 500 ml of 6.8 pH buffer medium with rotating speed at 50 rpm. Extrudates were removed after 1, 4, 8 and 20 hours, lightly blotted with tissue paper and then

reweighed (W2). The percentage increase in weight due to absorbed liquid was calculated from the following equation [26].

Swelling Index = (W2- W1)/W1 × 100 (7)

2.2.12 Matrix erosion study

A method performed matrix erosion studies similar to the reported paper by R. Malaviya [27]. After the swelling studies, the wet samples were then dried in an oven at 50°C for 24 h time period, followed by cooling in desiccator and finally weighed until constant weight was achieved (final dry weight, W2). The experiment was performed in triplicate for each time. The percentage matrix erosion at time (t) was estimated from the following equation.

ES = (W1-W2)/W1*100 (8)

3.3 Results and discussion:

3.3.1 Preliminary evaluation of HME vs Directly compressed tablet formulation

In order to check the effectiveness of melt extrusion over directly compressed (DC) tablet formulation, preliminary studies were carried out with DC tablets and melt extrusion method as described in **Table 1.** In DC tablet formulation the physical mixture of drug along with the used polymers in similar ration with the additives were prepared and compressed to tablets. Directly compressed tablet with same polymer ratio was compressed using Cadmach, a single punch tablet press (Batch B01 and B02). The hardness was kept at 18 kgf (8.0 kg/cm^2). These tablets were then used for the comparative studies with the formulations prepared by hot melt extrusion respectively. The extrudates were obtained at 140°C for S100 (B03) and 150°C for L100 (B04) combination. When polymer concentration was increased more than 50%, the extrusion was difficult to process due to high Tg of polymer. Therefore, the ratio of drug to polymer was fixed at 1:1 for further trials and analysis. In this, MSN acts as plasticizer for S100 and L100 polymer. The extrudates were manually cut into tablets as per MSN dose. The dissolution test was carried out as per USP/NF25. The dissolution profile of directly compressed tablets and extrudates formulations are shown in **Figure 1**. Extended release up to 20 hours was obtained in extrudates formulations. Incomplete (<50%) and slow release rate was observed with melt extrudate formulations. During HME production, the drug and polymer are melted, kneaded and

pressurized at the molecular level followed by the extrusion. Higher processing temperature reduced the polymer free volume of S100 and L100 and resulted in a denser and imperforate extrudates. This imperforate mass resisted the rapid penetration of dissolution medium into the matrix. Increase in the polymer concentration of S100 and L100 in HME process significantly retarded the release whereas, faster dissolution was observed when the polymer concentration decreased. 100% release was obtained within 1 hour with L100 and in 4 hours with S100 in conventional formulations. MSN at the surface of tablet dissolved immediately in dissolution medium and subsequently higher solubility of L100 and S100 at selected dissolution medium resulted in burst release. This indicates the superiority of melt extrudates over directly compressed tablets.

Combining polymers and release modifying agents with ionic charges has great importance in extending the release behavior of drug. Drug release can be modulated by forming interaction between PEO and poly(methacrylic acid-co-methyl methacrylate) L100 or S100 for site specific delivery of drug [28-30]. Diego Gallardo reported that combination of two different grades of Eudragit® polymers for development of new and modifying release delivery system [31], In another investigation, Mehta et al. developed a combination of L100-55 with S100 to achieve zero order release by method of extrusion spheronization [32]. L100-55 was used in combination with Eudragit® RSPO and RLPO [33] to modify the release of theophylline.

In order to achieve desired release profile with the same ratio of MSN and polymer extrudates, drug release modifying agent in combination with S100 and L100 was used during HME process. Directly compressed tablet with same ratio of polymers using single punch compression machine at 8 kg/cm3 pressure were prepared for comparative study.

All the batches were formulated as depicted in Table 1. Selective formulation batches like B07, B10, B13 and B16 were selected based on the uniformity of extrudes and dissolution performance. These batches were further characterized by analytical techniques such as FTIR, DSC, XRD and SEM for the evaluation.

3.3.2 Thermogravimetric analysis

The thermal stability of MSN, S100, L100, PEO303 and L100-55 was evaluated using Thermogravimetric analysis. The change in mass of the sample as a function of temperature was

analyzed in TGA.As illustrated in **Figure 2a**, 2% weight loss of MSN was observed at 188°C. In a previous study, it has been reported that MSN is stable below 160°C [34]. The L100, S100 and L100-55 were thermally stable up to 200°C as shown in **Figure 2**. Parekh T et al [35] investigated that the polymers S100, l100 and L100-55 are stable up to 176, 173 and 176°C respectively. Based on the stability profile of drug and polymer, the extrusion process should be carried out below the onset of degradation of all components.

3.3.3 Solubility Parameter

The calculated solubility parameters of MSN and combination of polymer are shown in **Table 2**. The value of S100: PEO303, L100: PEO303, S100: L100-55 and L100: volume fraction of each polymer calculated L100-55 mixture. The calculated difference (Δδ) between HSP (Hansen's solubility parameter) values of MSN and the mixture of polymer blend were found to be in the range 0.08 to 1.02 $MPa^{1/2}$. The δ values less than 7$MPa^{1/2}$indicated the likely miscibility of drug and polymer. Foster et al. [36] reported that compounds with Δδ<2 $MPa^{1/2}$ are likely to be miscible. On the contrary, the compounds with Δδ> 10 $MPa^{1/2}$ are likely to be immiscible.

3.3.4 HME extrusion process

PEO is a thermoplastic homopolymer synthesized by the heterogeneous catalytic polymerization of ethylene oxide monomer. It is highly water soluble and rapidly swells upon exposure to an aqueous environment to form a strong gel [37]. PEO303 with highest molecular weight is used in sustained release application. S100, L100 and L100-55 are anionic polymers based on poly(methacrylic acid-co-acrylates). L100 and S100 are differing in terms of their active Carboxylic group. Active carboxylic group in S100 is 29.2% whereas 48.3% in L100. This difference is responsible for their differing pH-dependent solubility. L100-55 is a copolymer of Methacrylic acid: ethyl acrylate. L100, S100 and L100-55polymers dissolve above pH 6.0, 7.0 and 5.5 respectively [35].

The ΔTg values between MSN and S100, L100, PEO303, L100-55 were 33, 55, 70 and 29°C, respectively. The Tg values of polymer S100 and L100 was decreased by the addition of L100-55 as calculated from GT equation 2 (**Table 3**). The Tg values of polymer combination calculated from GT equation are close to the melting of MSN for L100-55 combination and less

for PEO303 combination. Based on the properties of drug, polymer, stability and Tg predicted from GT equation, the extrusion trials were performed at 115°C with PEO303 and 140°C with L100-55 combination. The formulation batches of MSN with S100: PEO 303 (B05–B07), with L100: PEO 303 (B08–B10),with S100: L100-55 (B11–B13) and with L100: L100-55 (B14–B16)are shown **Table 4.** Plasticizers are often included in HME formulations to improve flexibility and workability, as this allows lower production temperature due to decrease in melt viscosity and shear forces. In this study, no plasticizers were used in order to check the plasticizing effect of PEO303 and L100-55 on extrusion process ability and dissolution.

When extrusion was processed at higher temperature (140°C) resulted in molten and sticky extrudates. Whereas, an uniform extrudates with PEO303 was obtained at 115°. Due to low glass transition temperature of PEO303, it melts well before the melting point of drug and S100, L100. In this, the drug and polymer are embedded in PEO303 polymer matrix. Whilst, in combination with L100-55 processed at 140°C, a transparent and uniform extrudates was obtained. The extrusion processed well before the Tg of S100 and L100 indicates the plasticization effect of PEO303 and L100-55 on these polymers. An intimate mixing at elevated temperature during HME process resulted in drug/polymer interaction, allowing drug to occupy active sites along the polymer chains and reduces polymeric inter-chain interactions. This resulted in reduced processing temperature. The uniform formulation was used for further characterization and dissolution study.

3.3.5 Stability of Extrudates

The obtained extrudates were further analyzed by TGA for thermal stability of extrudates (**Figure 2b**). A 2% weight loss at 167.94 and 170.74°C in PEO303 and L100-55 combination respectively exhibited the stability of extrudates at processing temperature. Therefore, it was concluded that the processing temperature studied were suitable during the extrusion process. Drug content uniformity was performed with pure MSN, extrudates of batch B07, B10, B13 and B16 using HPLC. A minor (± 2.0%) change in the chromatogram of MSN was observed in formulation extrudates. The observations revealed that there is no chemical degradation after thermal processing. Also, the drug content was approximately between 98 to 100 % (HPLC graph are not shown).

3.3.6 FT-IR Spectroscopy

Drug interaction between drug and polymer in solid dispersion was evaluated with FT-IR study. The FT-IR spectra of MSN, PEO 303, S100, L100, L100-55, batch B07, B10, B13 and B16 are shown in **Figure 3**. FT-IR analysis revealed the stretching vibration of –OH and functional –NH in MSN at 3691 and 3148.5 cm^{-1}respectively. Other peaks are C-H stretching at 2923.23 cm^{-1}, C≡C aromatic stretching vibration at 1562.06 cm^{-1}, C-O stretching at 1385.67 cm^{-1}, C-N stretching at 1241.99 cm^{-1} and C-O-C stretching vibration at 1113.89 cm^{-1}. PEO 303 showed broad and intense peak at 3527 cm^{-1} confirms the presence of –OH group. Strong stretching vibration and broad bands of –OH in S100 and L100 was observed at 3548.50cm^{-1} and 3531.68 cm^{-1}respectively.The wide absorption range of the associated OH groups between 2,500 and 3,500 cm-1 is superimposed by -CHx(where x = 1, 2, 3..) vibrations at 2,900 - 3,000 cm^{-1}. The characteristic peak of hydroxyl group (-OH) in L100-55 was obtained in the range of 3475.16 and 2359.12 cm^{-1}. The bands of methyl and methylene (CH stretch vibration) at 2975.18 cm^{-1} and 2895.16 cm^{-1}, strong band due to carbonyl group (C-O) at 1734.12 cm^{-1} and two bands due to ester linkage (C-O) at 1367.4 cm^{-1} and 1267.1 cm^{-1} were observed in L100-55.

The used carriers PEO 303, S100, L100 and L100-55 have –OH and C=O that may react with above groups of MSN. Any interaction between the above functional group results from the possible hydrogen bonding between drug and polymers which leads to frequency shifts or splitting in absorption peaks. As can be seen from the **Figure 3**, the characteristic peak intensity of C=O from S100 and L100 was lowered in PEO 303: L100 and S100 (Batch B07 and B10). The intensity at 1730 cm^{-1} was lowered in S100 formulation compared to L100. This indicates the stronger interaction occurred with S100: PEO303 formulation compared to L100: PEO303. Also, the peak intensity between 2500cm^{-1} and 3500cm^{-1} decreased. The -OH peak intensity from MSN disappeared in PEO303 formulation indicates the interaction between C=O from S100, L100 from carboxylic acid and -OH from MSN. A hydrogen bond formation was occurred in PEO303 formulations. The –OH stretching bands of MSN and carboxylic acid broad band between 3200-2500 cm^{-1} and at 1730 cm^{-1} were completely decreased and disappeared in formulation B13 and B16. This indicates the formation of non-crystalline dispersion of MSN in L100-55 combinations with S100 and L100. The C=O in S100, L100 and L100-55 forms

hydrogen bond with –OH group of MSN. This exhibited the intermolecular interaction between MSN and S100, L100 thorough HME process.

3.3.7DSC studies

DSC studies were performed to assess the crystallinity of drug into the polymer structure. The DSC thermogram of MSN, S100, L100, PEO 303, L100-55, extrudates of B07, B10, B13 and B16 are shown in **Figure 4**. The DSC profile of MSN showed the endothermic peak at melting point of 140°C. Semi-crystalline nature of PEO303 exhibited endothermic peak at 70°C. The thermogram of S100 displayed two broad melting events which represented the evaporation of unbound water between 50°C and 100°C, followed by a second melting event at 172°C, attributed to the amorphous nature of S100. L100 showed glass transition temperature above 190°C. The change in Tg values of S100 and L100 was due to differences in monomer ratios, i.e 1:2 or 1:1 between methacrylic acid and methacrylate. The change in glass transition temperature of L100-55 was observed at 117°C.

The presence of single Tg and absence of endothermic melt for the drug (140°C) were indicated that the drug was homogenously dispersed in non-crystalline state in polymer matrix. A broad peak with melting point depression at 112 and 118°C in batch B07 and B10 indicates the semi-crystalline nature of MSN in PEO303: S100 and L100 matrix at 115°C extrusion temperature. As discussed earlier, PEO303 melts well before the MSN and other polymer melts which depicted broad endothermic peak of MSN. A single peak was obtained with PEO303 formulation which was produced at 140°C. This indicates the non-crystallinity of drug at 140°C extrusion temperature. No endothermic peak of MSN was obtained in formulation with L100-55: S100 and L100. This indicates the homogeneous dispersion of non-crystalline drug in polymer matrix.

3.3.8 XRD study

MSN exhibited two sharp peaks at 2θ equal to 13.7 and 20.2 and a series of small peaks at 7.2 and 23.7 as shown in **Figure 5**, indicating crystalline nature of drug. The PEO 303 is a semi-crystalline polymer and showed highest crystalline peak at 23.5. A smaller, distinct peak was also observed at 19.1 in PEO 303. The S100, L100 and L100-55 were devoid of sharp peaks and displayed broad halos. It confirms the amorphous nature of Eudragit® polymer. In the case ofmelt extruded with PEO 303 (B07 and B10), the characteristic peak of MSN and PEO 303 was

observed. The low intensity in B07 and B10 indicates the semi-crystalinity of MSN. The reduction in intensity was associated with a decrease in crystallinity and the peaks become broader due to wider distribution of crystal sizes. Whereas, the characteristic peak of MSN in extrudates with L100-55 combinations were devoid of sharp peaks and showed broad halos. Formulation with L100-55 with S100 (B13) and L100 (B16) confirms the non-crystalline nature of MSN after HME process. In contrast semi-crystalline nature of MSN was observed with PEO 303 with S100 and L100 polymers. The results are in accordance with DSC studies.

3.3.9 SEM Analysis

SEM micrographs of extrudates gave surface morphology information. SEM micrographs of extrudates with PEO303 and L100-55 are shown in **Figure 6**. From the SEM micrograph, it was evident that prepared formulations resulted in a significant particle size reduction. Formulations B07 and B10 revealed rough surface morphology without sharp edges. The SEM of formulations appeared to be agglomerated with rough surface owing to the presence of polymer. However, extruded systems have smaller particle size, relatively rough surface; suggest that hydrophilic polymer and PEO were spread uniformly on the surface of the drug**.** SEM micrographs of formulations with L100-55 (B13 and B16) (Fig 6 c-d) exhibited transparent and homogenous surface. The absence of crystalline nature of MSN confirms the uniform distribution of drug in polymer matrix. These results are in agree with the DSC and XRD results which confirms the semi-crystalline nature MSN in PEO 303 matrix and non-crystalline in L100-55 matrix system.

3.3.10 In-Vitro dissolution studies

The polymer used in this study are pH sensitive, therefore the dissolution was carried out in 0.1N HCL followed by in 6.8 pH buffer.

Influence of PEO 303 on S100 and L100 matrix

Figure 7 (a) and (b) illustrated the dissolution profile of MSN in combinations with PEO303: S100 and L100. No sustain release or enteric effect can be seen with a drug release of more than 40% with S100 and L100 in combination with PEO303 in the first 2 hours in 0.1 N HCL. 100% release was obtained within 11 hours of dissolution study in subsequent pH 6.8 which included 2 hours in 0.1 N HCl and 5 hours in pH 6.8 with PEO303: L100 combination. Whereas, complete release was not obtained until 15 hours with S100: PEO303 combination of dissolution testing at

pH 6.8 including 2 hours in 0.1N HCl. The faster drug release in the 6.8 pH of PEO303: L100combination was due to higher pH dependent solubility of L100 at 6.8 pH. Whereas, the extended release with PEO303: S100 combination was due to lower solubility of S100 at selected dissolution medium. As discussed earlier, S100 started to dissolve at pH 7.0.A gradual increase in the dissolution rate was observed with the increase in the concentration of PEO303. A rapid higher dissolution rate was obtained when extrudates were immersed at higher pH 6.8.

It was observed from the **Figure 9** that the addition of hydrophilic PEO303 in S100 and L100 combination increased the MSN release in 0.1N HCl. The hydrophilic polymer PEO303 changed the drug release rate by increasing the drug diffusivity in the matrix although S100 and L100 are insoluble in acidic media. (38). It was also observed that, slight increase in dissolution rate in 0.1N HCL was obtained with L100 than S100 combination. Though S100 and L100 are insoluble in 0.1N HCl, the diffusion of drug was higher with L100: PEO303 combination in 0.1N HCl. A decrease in cumulative percentage release was observed as soon as the extrudates were placed in 6.8 pH. In order to confirm any interaction occurred at pH 6.8 in dissolution, FT-IR of extrudates from 0.1N HCl followed by pH 6.8 has been taken and showed in **Figure 8**. No change in peak intensity was observed which could be concluded as no complexation formed in pH 6.8. The decrease in drug release at pH 6.8 can be explained as formation of entangled network between PEO303 and L100, S100 that reduced the erosion rate of the tablet. A further gradual decrease in the release rate of MSN was due to the hydration of the hydrophilic polymer present in the matrix (39).

The dissolution of the all formulations was also performed separately in pH 6.8 as per USP/NF dissolution test for MSN and are shown in **Figure 9 (a)**. A gradual increase in dissolution rate was observed with higher concentration of PEO303 in combination with S100 and L100.Change in dissolution rate with change in concentration of PEO303 in combination with S100 was observed whereas no significant change in dissolution rate was observed with L100: PEO303 combination. On exposure to dissolution medium, the extrudates surface becomes wet and starts to hydrate to form a viscous gel layer. The release of the drug from the extrudates can be governed by the diffusion and its subsequent erosion. The linear behavior in these matrices can be explained by keeping the diffusion path length constant during drug release as that matrix erosion was balanced with swelling of the matrix. The swelling of PEO303 and erosion of L100

at 6.8 pH was occurred simultaneously due to higher solubility of PEO303 and L100 at pH 6.8. However, due to lower solubility of S100 at pH 6.8, erosion was not occurred with higher concentration of S100 whereas at lower concentration of S100, PEO303 swells and erode which resulted in faster release rate.

Release mechanism

Drug release data from the dissolution investigation of extrudates (11.0 mm × 4.0 mm) in either 0.1N HCl or pH 6.8 were used for the model fitting. As shown in **Table 5 (a).** Correlation coefficient (r^2) greater than 0.99 was obtained in PEO303 with S100 and L100 combination, which fitted the model well. All the formulation following non-Fickian mechanism in 0.1N HCl as well as in 6.8 pH. This means that the drug release followed both diffusion and erosion mechanism. All formulation followed non-Fickian mechanism in 0.1N HCl due to nearly equal concentration of swelling agent PEO303 compared to S100 and L100. This increases the diffusivity in the matrix in the medium where S100 and L100 are insoluble in 0.1N HCl. The release exponent ranged from 0.49 to 0.66 in both pH with S100 and L100 was controlled by a combination of matrix erosion and diffusion of the drug in hydrated polymer matrix.

Influence of L100-55 on S100 and L100 Matrix

Figure 9 (b) depict the release profile of MSN matrix containing L100-55: S100 (B11-B13) and L100-55: L100 (B14-B16). The extrudates of MSN released was not more than 3 % at the end of two hours in 0.1N HCL. In the following pH 6.8, MSN was released slowly. Differences in release profile of MSN were observed in all extrudates. The dissolution rate decreased significantly with the addition of S100 in the formulation B11. However, increase in the concentration of L100-55 resulted in higher release of MSN in batch B12. A direct relationship is apparent between the decrease in the dissolution rates and increase in the L100-55 contents in the formulations. A higher and complete dissolution rate in all formulations with L100 and L100-55 can be explained as the higher solubility of both the polymers at selected pH 6.8. As shown in **Figure 9 (b)**, higher dissolution rate was observed with all formulations of L100: L100-55 (B14 to B16). Introduction of L100-55 does not affect in the dissolution rate with L100 formulations. Whereas, a linear relationship in S100: L100-55 formulations can be explained as the gradual dissolution of these polymers at pH 6.8.

The dissolution profile of the extrudates of formulation B13 and B16 has been simulated with the conventional models (**Table 5 (b)**). The highest related coefficient, The Hixon crowell equation seemed to be suitable. A decrease in the dimension of extrudates with time was observed in B13 and B16. However, a significant decrease in mass and the dimension of extrudates were not observed. Hence the dissolution mechanism in extrudates can be explained as due to pore formation in the extrudates as a result of faster solubilization of L100-55 than S100 and L100 at the selected pH. The higher the amount of L100-55 in the formulation, the weaker point or pore may have formed thus creating the channels for dissolution media to penetrate into the extrudates resulting in higher dissolution.

Swelling and erosion study

In order to determine the influence of gelling agent on the mechanism of drug release from melt extudates, the swelling and erosion of the matrix tablets during dissolution were investigated. The results of these studies supported the findings of fitting to the Korsmeyer-Peppas model. **Figure 10** illustrate the swelling and erosion of batch B07 and B10. Drug release was initially through diffusion as well as erosion controlled in 0.1N HCl with S100 and L100 in combination with PEO303. The higher concentration of PEO303 in all formulation resulted in swelling and erosion in the presence of S100 and L100. The swelling and erosion was occurred simultaneously with formulations containing L100-PEO303. The rate of erosion increased when formulation containing L100-PEO303 were added in pH 6.8. The swelling and erosion was proportionally increased and decreased respectively in formulation containing S100: PEO303. The higher solubility of L100 at pH 6.8 compared to S100 resulted in higher swelling and erosion during dissolution in the presence of PEO303 hydrophilic polymer. The lower solubility of S100 at selected dissolution pH maintained the shape and integrity of extrudates during dissolution and was mainly responsible for lower erosion rate as compared to L100. The higher solubility of L100 at pH 6.8 with higher swelling of PEO303 was unable to maintain the integrity of extrudates which resulted in higher dissolution rate.

3.3.11 Comparison with marketed Formulation

The optimized formulation B12 was compared with marketed formulation Actiblok IPR 100 from Biocon and Betaone XL100 from Dr. Reddy's Lab in terms physicochemical characterization. In order to control the release of MSN, the concentration of excipients requires

5 to 6 times for marketed formulation. However, it required 1-fold concentration of excipients for B13 through HME process. Also, it avoids many steps involved in conventional dosage formulation. The dissolution profile of marketed product and optimized formulation are shown in **Figure 11.** The dissolution profiles of B12 are matched with marketed Actiblok IPR100 from Biocon with similarity factor F2 as 72.36. 100 % release was obtained in Betaone XL100 tablet.

4.4 Conclusion

Stabilized extended and enteric release preparation can be produced by the HME technology. Drug was dispersed in amorphous state at melting temperature of MSN. But found in semi-crystalline state at lower extrusion temperature. Drug release can be modulated with addition of PEO303 and L100-55. The difference in dissolution rate between PEO303 and L100-55 was due to inherent nature of individual polymer. The hydrophilic and swelling behavior of PEO303 resulted in faster release through swelling and erosion mechanism and solubility of S100 and L100, whereas sustained and enteric behavior in tablets from L100-55 came from diffusion mechanism. Formulation B12 with minimum concentration of S100: L100-55 in the same ratio was able to extend the release with F2 value of 76% compared to marketed product Actiblock IPR 100. Based on the above observation, it can be concluded that L100-55: S100 polymer combinations are better suited over PEO 303: S100 and L100 in terms of physical state and dissolution rate for the development of extended release formulation of MSN through HME process.

Acknowledgments

The author is also thankful to UGC (SAP) for providing the research fellowship and Institute of Chemical Technology, ELITE status (Mumbai, India) for providing all facilities and guidance.

Declaration:

Authors declares that there is no conflict of interest.

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Figure Legends

Figure 1 Dissolution profile of conventional tablets and extrudates formulations

Figure 2a depicts TGA analysis of MSN, S100, L100, PEO303 ,L100-55 and

Figure 2b depicts TGA studies of extrudate formulation

Figure 3 FT-IR spectra of MSN, PEO 303, S100, L100, L100-55, batch B07, B10, B13 and B16

Figure 4 Showed DSC profile of MSN and extrudes

Figure 5 Showed XRD profile of MSN and extrudes

Figure 6 SEM micrographs of extrudates gave surface morphology information

Figure 7 Dissolution profile of MSN in combinations with PEO303: S100 and L100

Figure 8 IR studies after addition of hydrophilic PEO303 in S100 and L100 combination

Figure 9a Dissolution studies with different combination with S100 and L100 from B05 to B10

Figure 9b Depict the release profile of MSN matrix containing L100-55: S100 (B11-B13) and L100-55: L100 (B14-B16)

Figure 10 Illustrate the swelling and erosion studies of batch B07 and B10

Figure 11 Dissolution profile of marketed product and optimized formulation

Figure 1

Click here to download Figure Figure 1.jpg

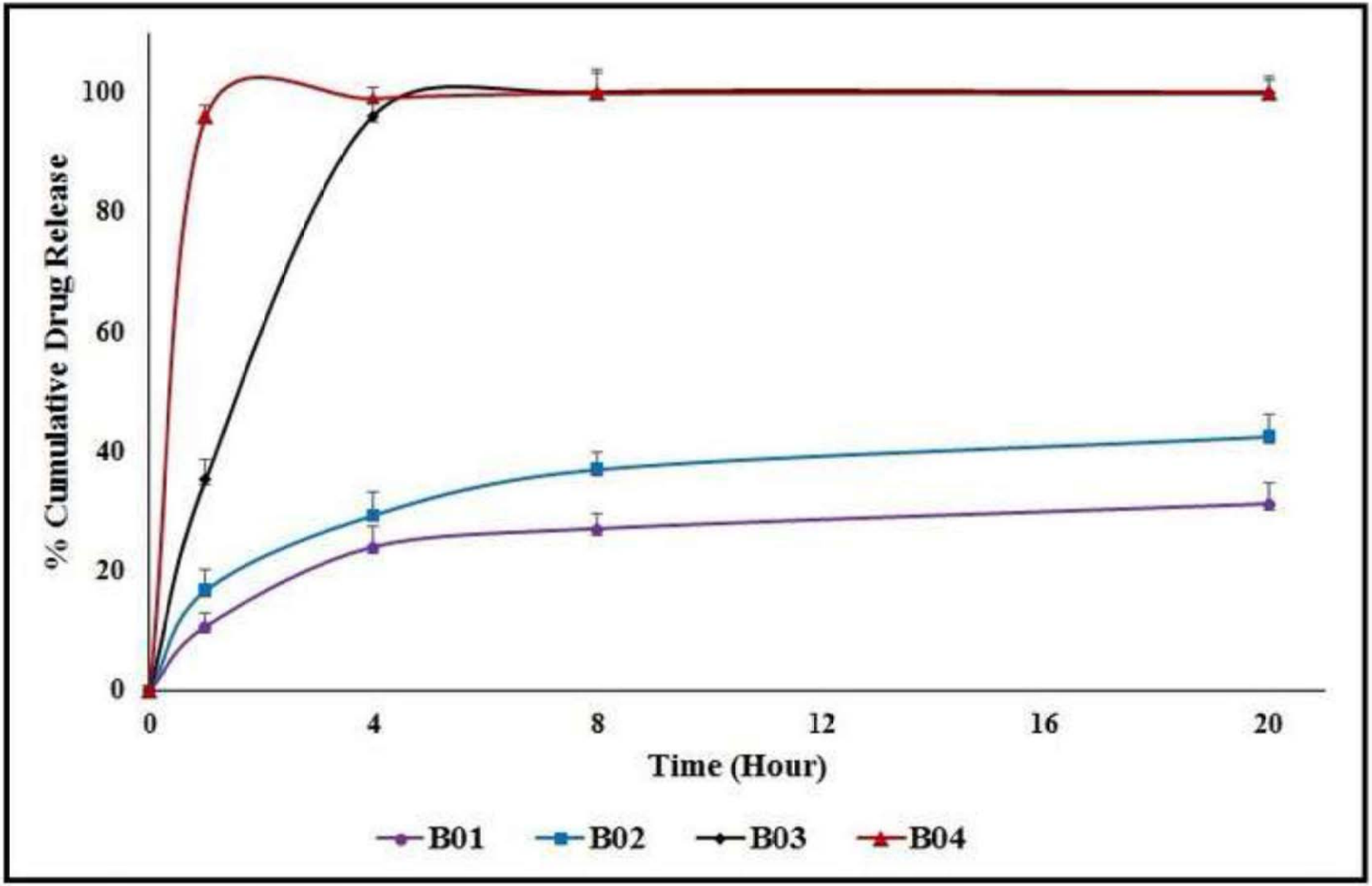
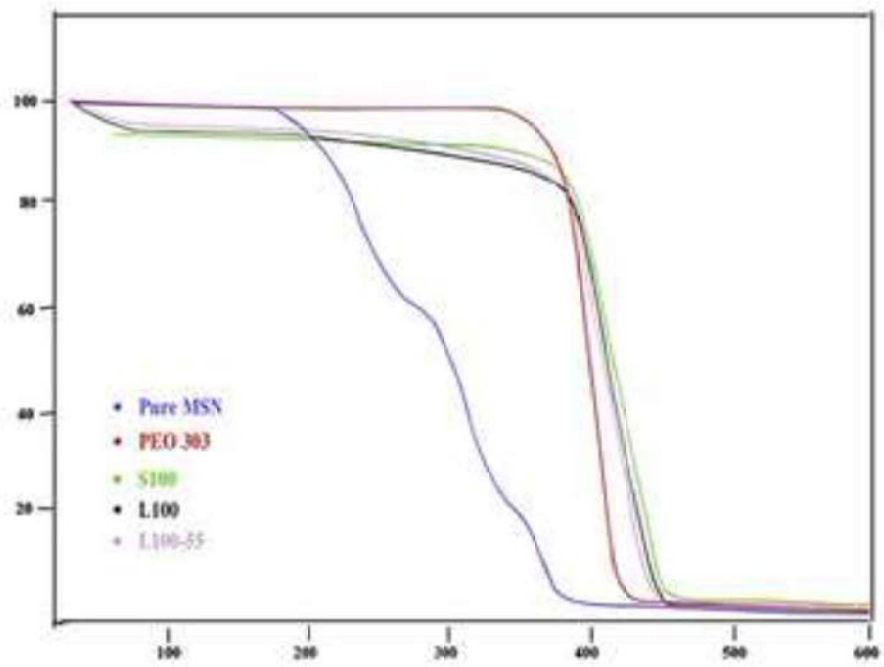


Figure 1 Dissolution profile of conventional tablets and extrudates formulations

Figure 2

Click here to download Figure Figure 2 a and b.jpg



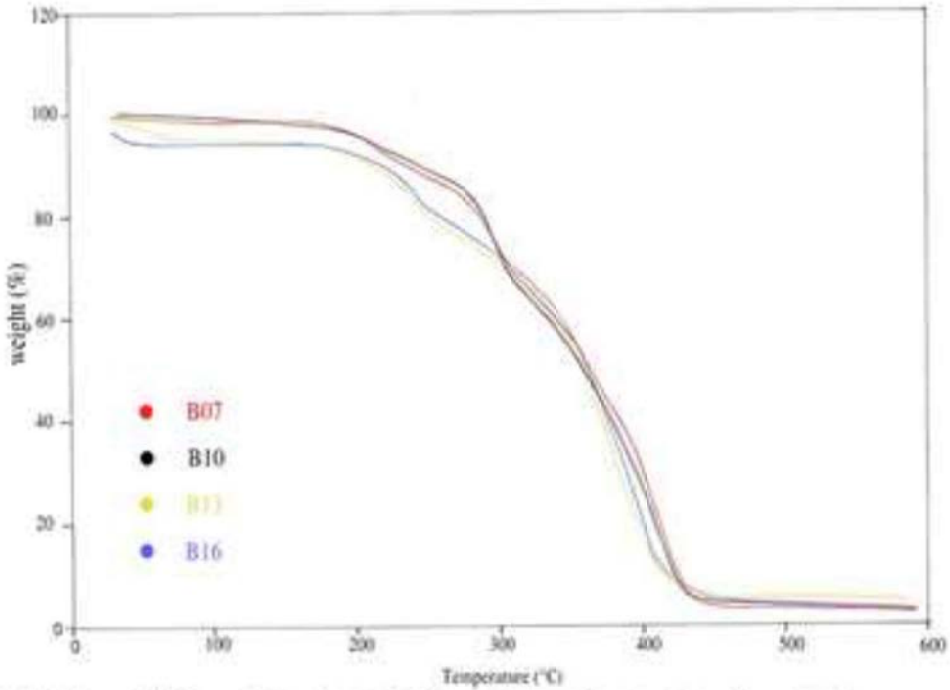


Figure 2a depicts TGA analysis of MSN, S100, L100, PEO303 ,L100-55 and **Figure 2b** depicts TGA studies of extrudate formulation

Figure 3

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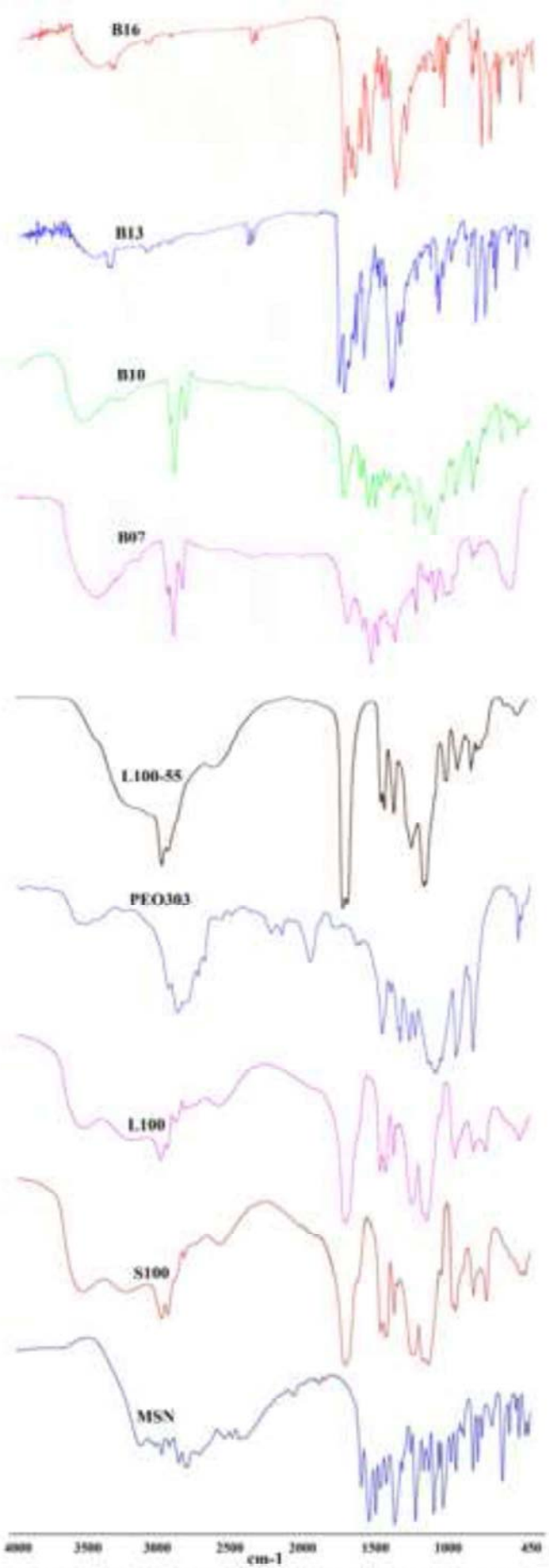


Figure 3 FT-IR spectra of MSN, PEO 303, S100, L100, L100-55, batch B07, B10, B13 and B16

Figure 4 Click here to download Figure Figure 4 DSC extrudates.jpg

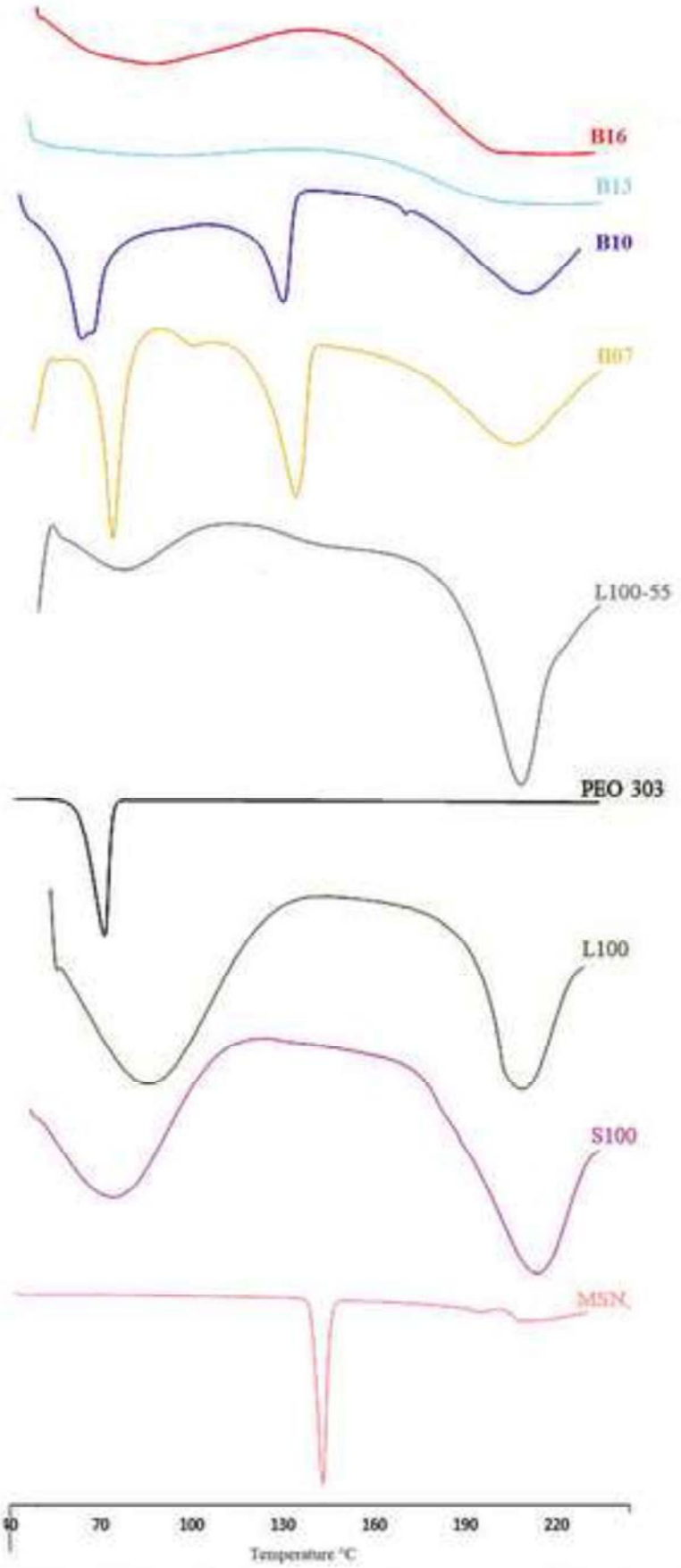


Figure 4: DSC analysis of MSN, S100, L100, PEO303, L100-55 and extrudates of B07, B10, B13 and B16

Figure 5

Click here to download Figure Figure 5 XRD.tif

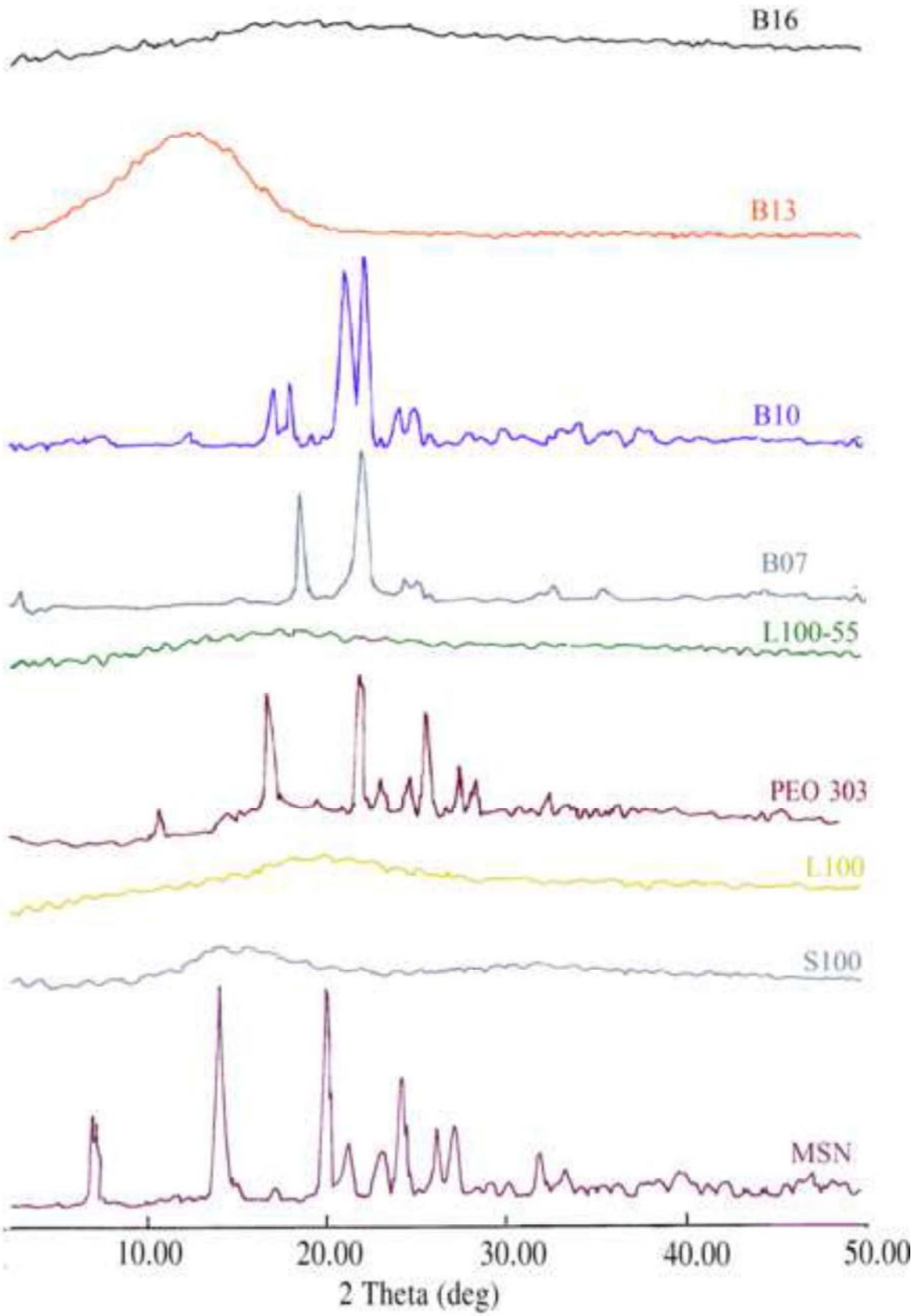


Figure 5: XRD analysis of MSN, S100, L100, PEO303, L100-55 and extrudates of B07, B10, B13 and B16

Figure 6

Click here to download Figure Figure 6 SEM.tif

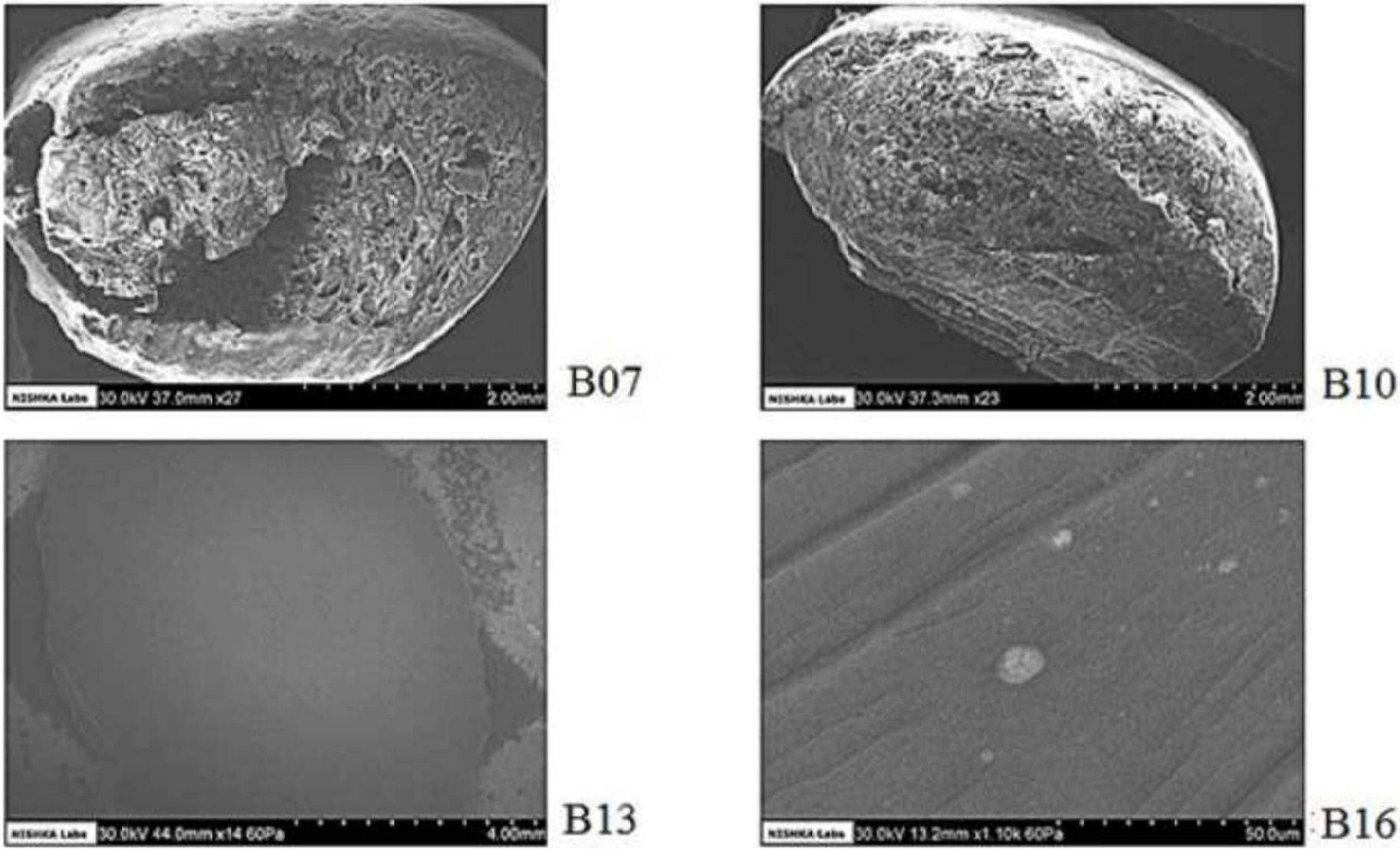
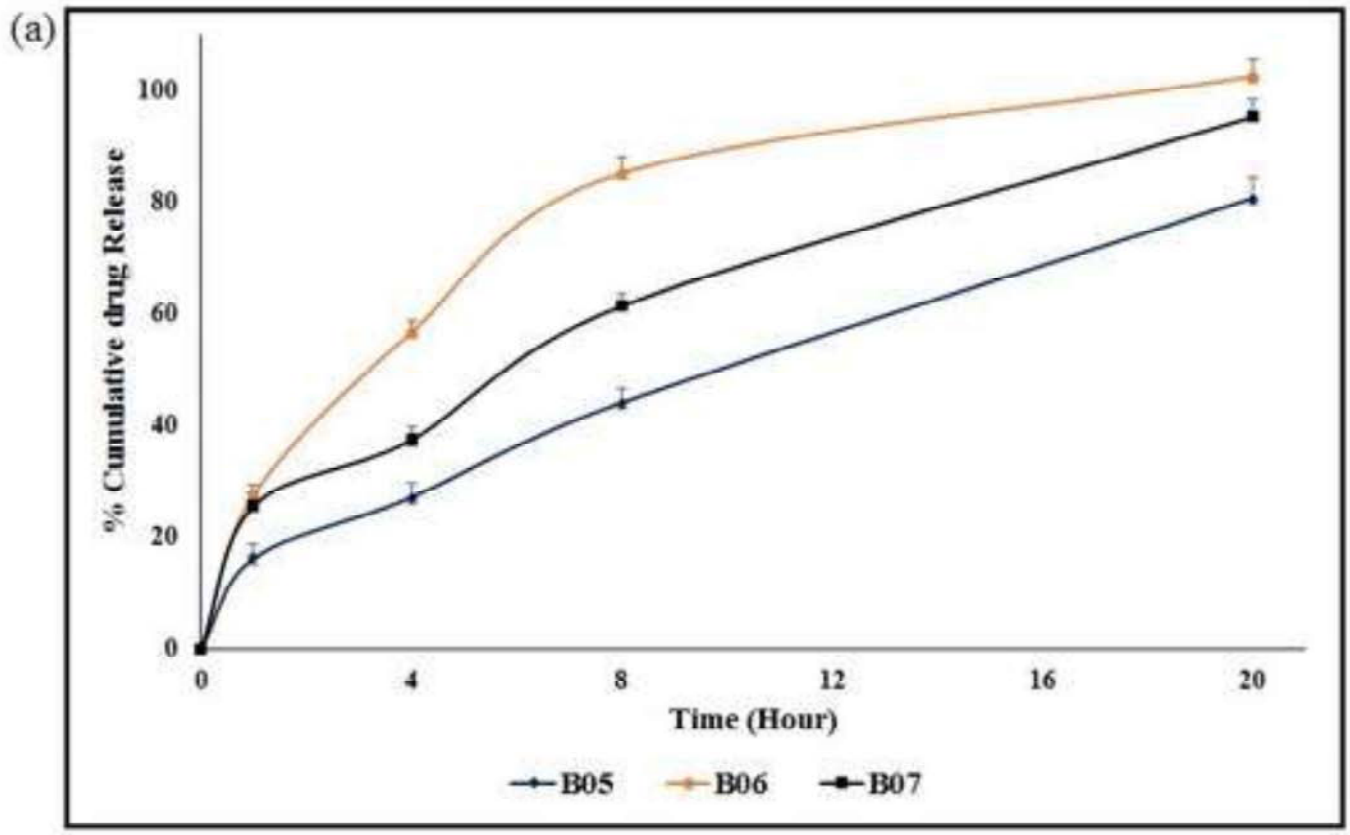


Figure 6: Extrudates SEM images of B07, B10, B13 and B16

Figure 7

Click here to download Figure Figure 7 B05 to b10 in 6.8 pH.jpg



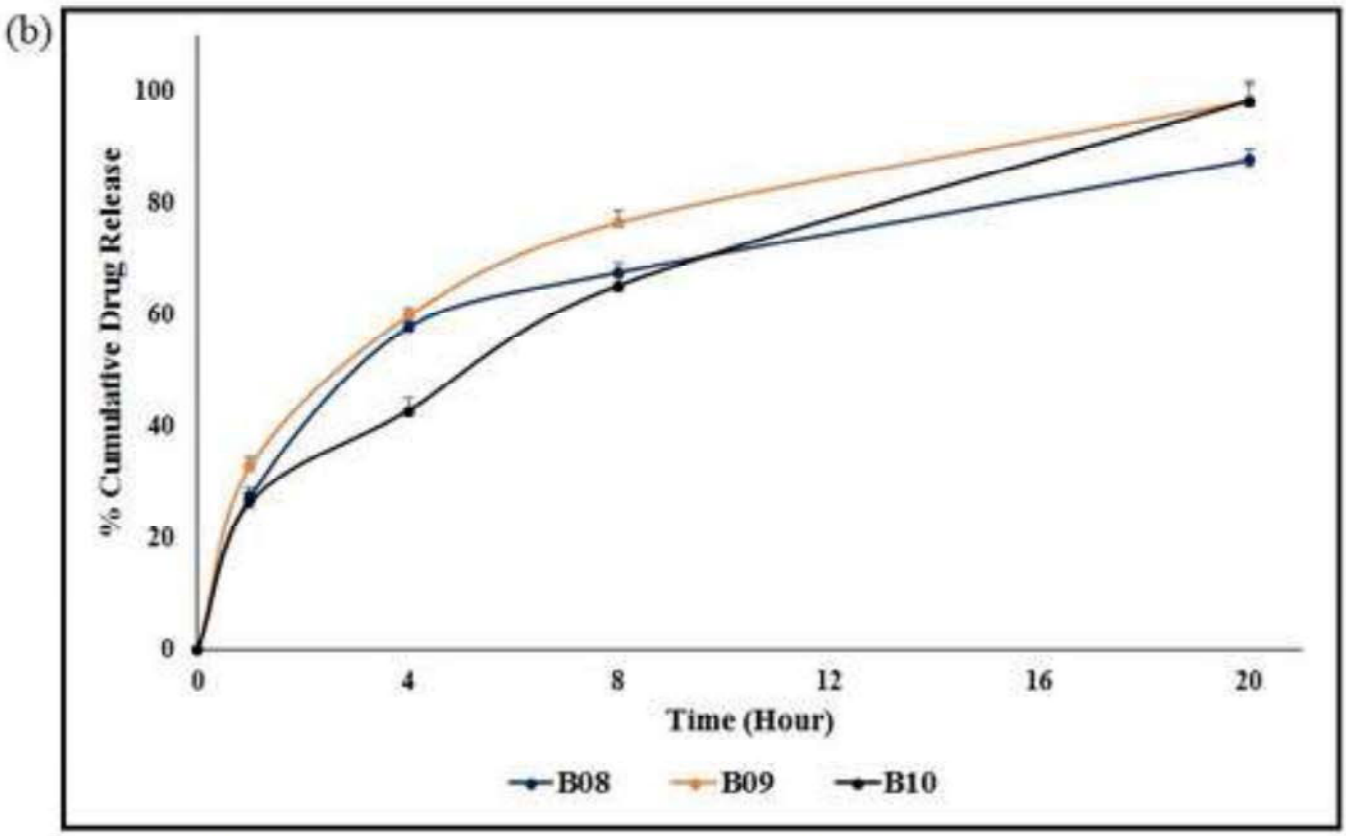


Figure 7 Dissolution profile of MSN in combinations with PEO303: S100 and L100

Figure 8

Click here to download Figure Figure 8 IR.tif

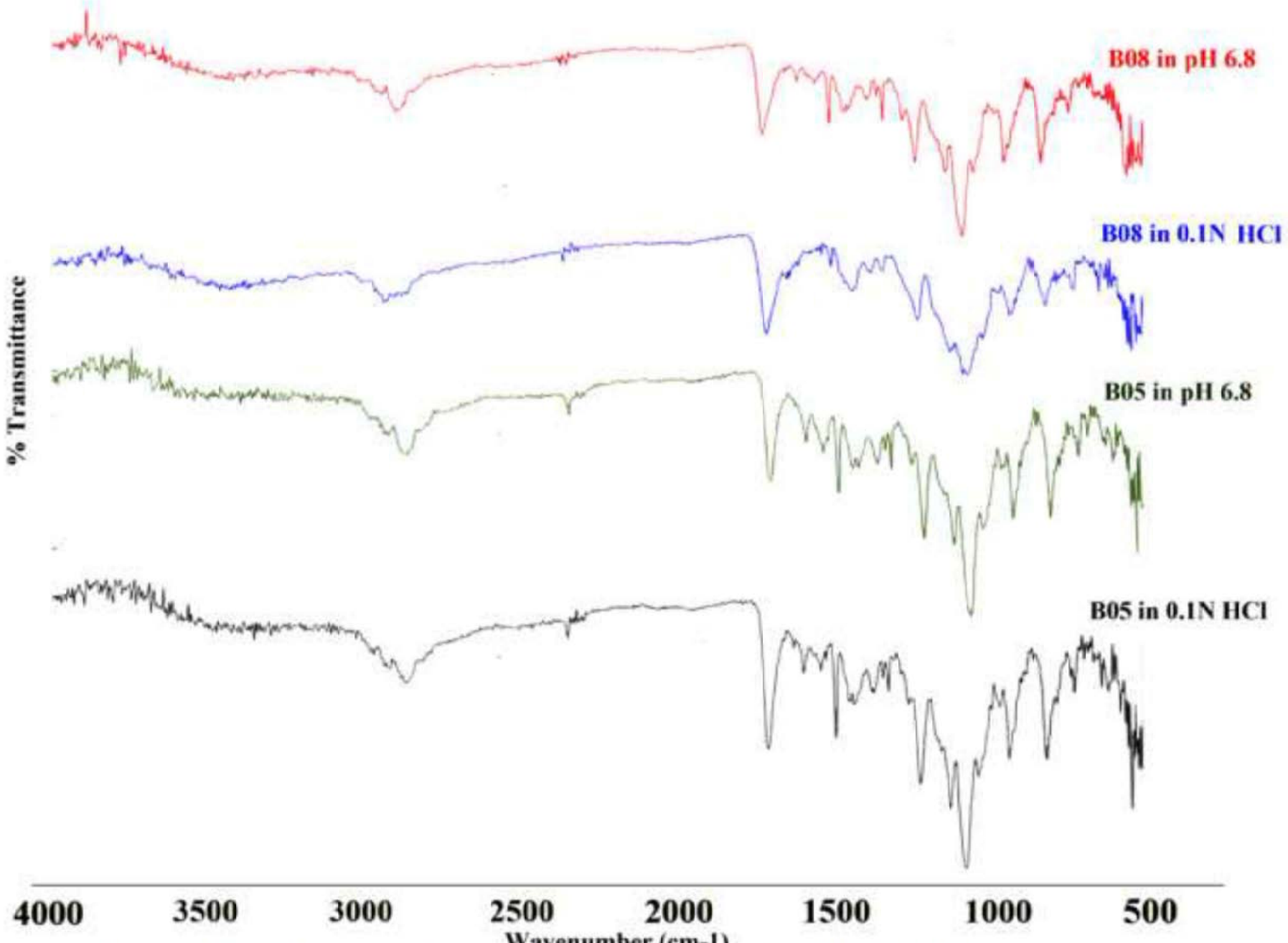
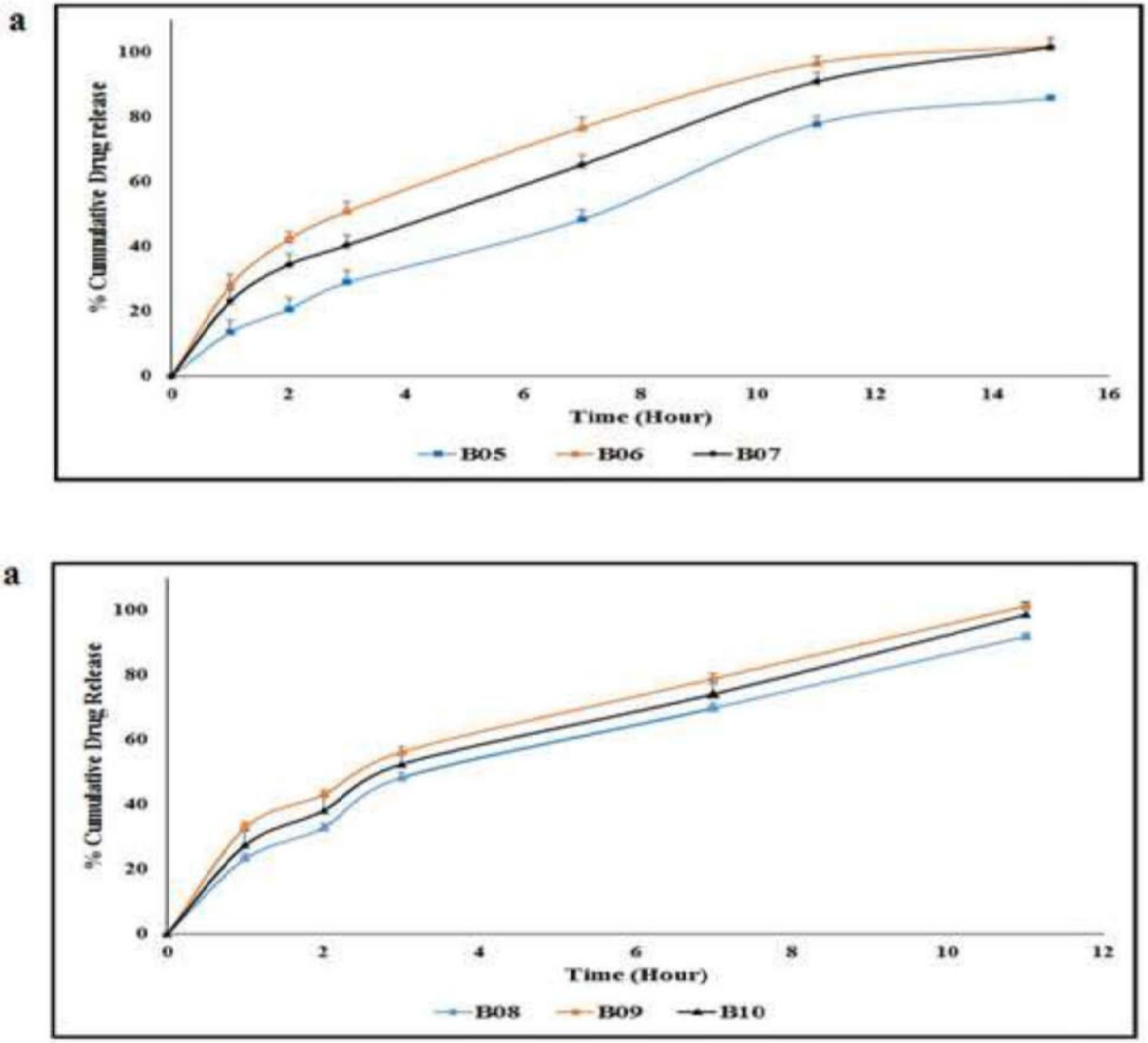


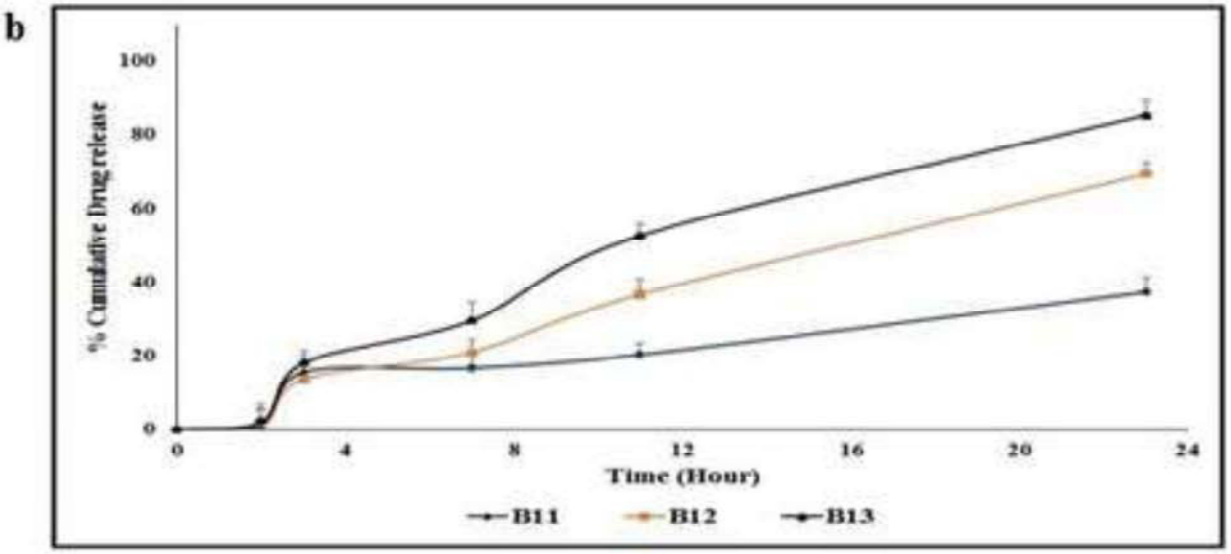
Figure 8 IR studies after addition of hydrophilic PEO303 in S100 and L100 combination

Figure 9a



9a Dissolution studies with different combination with S100 and L100 from B05 to B10

Figure 9b



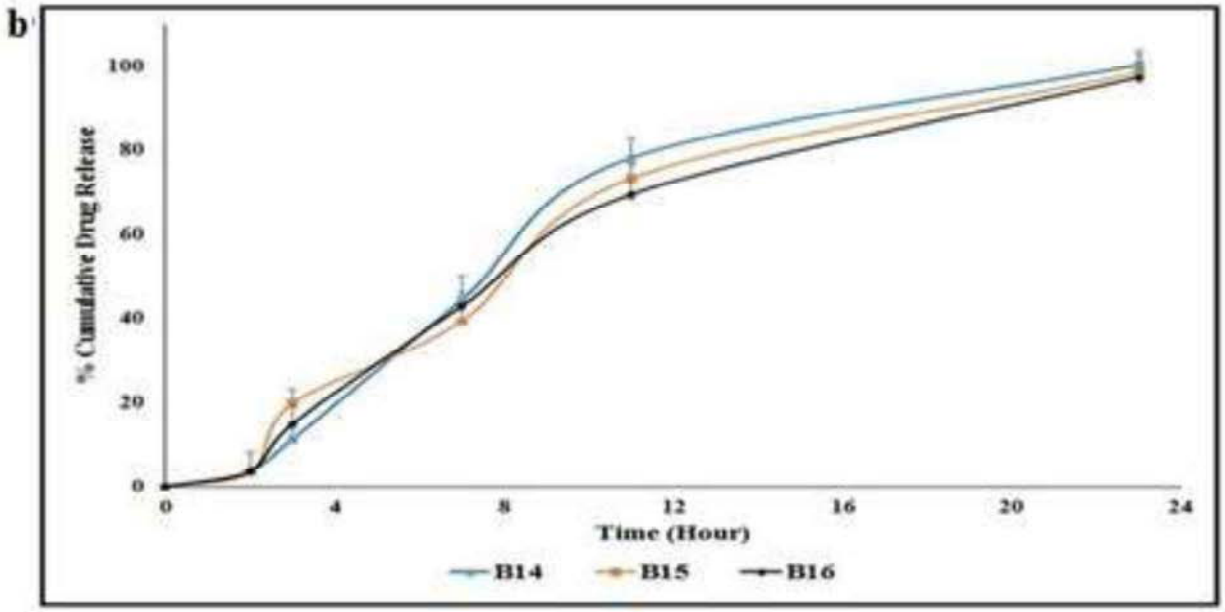


Figure 9 (b) depict the release profile of MSN matrix containing L100-55: S100 (B11-B13) and L100-55: L100 (B14-B16).

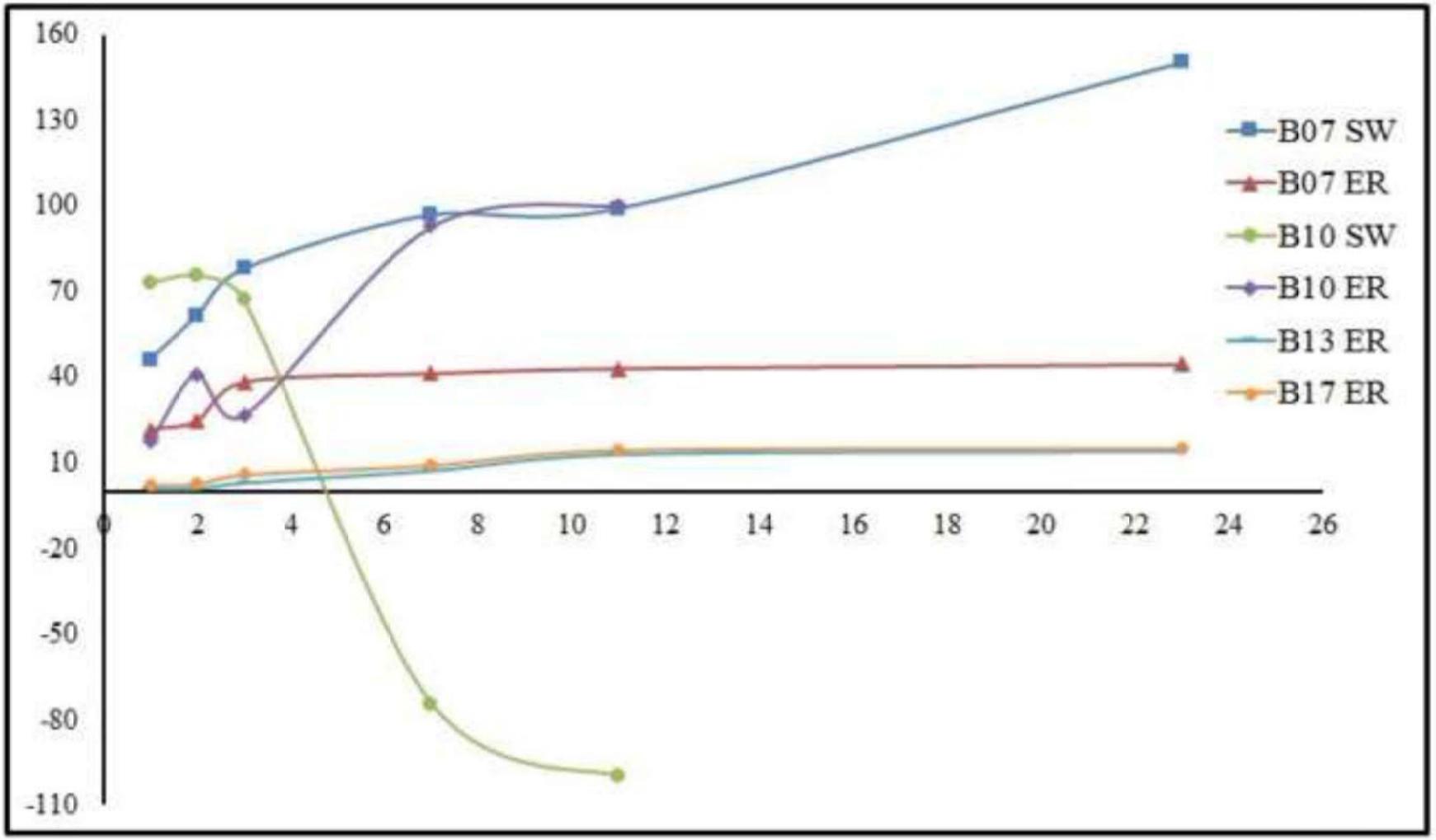


Figure 10: Swelling and erosion study of B07, B10, B13 and B17 in 0.1N HCl followed by in 6.8 pH buffer

Figure 11

Click here to download Figure Figure 11 New Marketted Disso.jpg

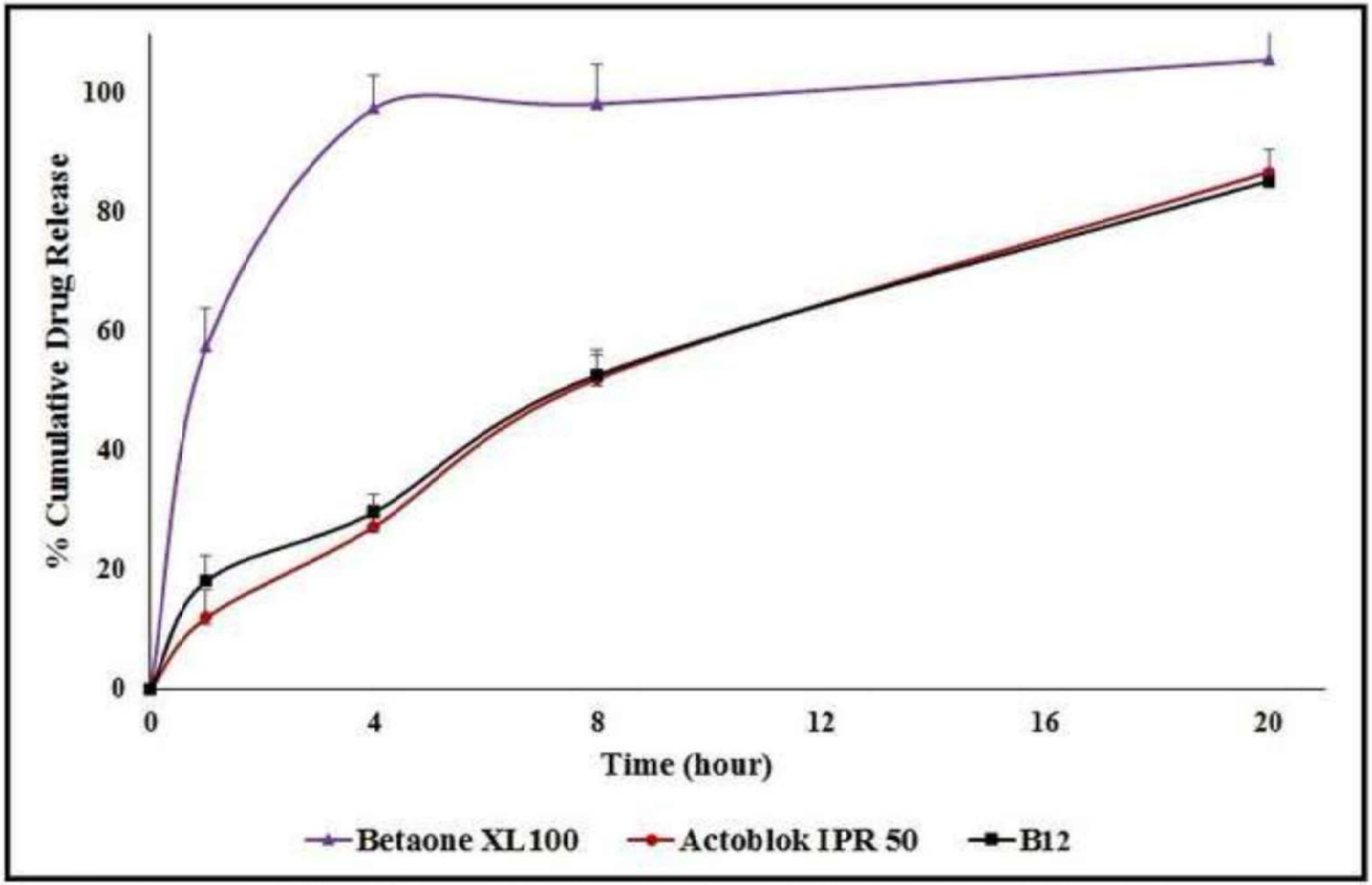


Figure 11 Dissolution profile of marketed product and optimized formulation

Table Legends

Table 1: batches with HME and conventional compression method

Table 2: Solubility parameter calculation for drug polymer compatibility

Table 3: Tg estimation of polymer combination from Gorden Taylor Equations

Table 4: batches of MSN S100 and L100 in combination with PEO 303 and L100-55

Table 5 (a): Korsemeyer-peppas model fitting of dissolution data from B07 and B10

Table 5 (b): Simulated model for release profile of batch B13 and B16

Table 1

Table 1: batches with HME and Direct compression method

Batch	B01	B02	B03	B04
	Conventional method		HME method	
MSN	95	95	95	95
S100	100	--	100	--
L100	--	100	--	100
Total	195	195	195	195

All the quantities are expressed in mg

Table 2

Table 2: Solubility parameter calculation for drug polymer compatibility

Drug and Polymer	δ_{hi}	δ_{di}	δ_{pi}	δ	$\Delta\delta$ MPa$^{1/2}$(Not ≥7	Drug polymer compatibility
MSN	18.06	2.32	11.77	21.68 (a)	---	---
S100 + PEO 303 (1:1, w/w)		(21.1+22.0)/2		20.55 (b)	(a – b) = 1.13	Miscible
L100 + PEO 303 (1:1, w/w)		(22.9 + 22.0)/2		21.45 (c)	(a – c) = 0.23	Miscible
S100 + L100-55 (1:1, w/w)		(21.1 + 22.5)/2		21.8 (d)	(a – d) = 0.12	Miscible
L100 + L100-55(1:1, w/w)		(22.9 + 22.5)/2		22.7 (e)	(a – e) = 1.02	Miscible

Table 3

Table 3: Tg estimation of polymer combination from Gorden Taylor Equations

Formula Codes	W1	Tg1	w1Tg1	W2	Tg2	W2 Tg2	ρ1	ρ2	K	(w1Tg1 + K1W2Tg2)	(w1 + K1w2)	Tg mix
B05	55	173	9515	45	70	3150	1.189	1.13	2.5996	17704	171.98	102.94
B06	45	173	7785	55	70	3850	1.189	1.13	2.5996	17793	187.98	94.657
B07	50	173	8650	50	70	3500	1.189	1.13	2.5996	17749	179.98	98.614
B08	55	195	10725	45	70	3150	1.19	1.13	2.9346	19969	187.06	106.75
B09	45	195	8775	55	70	3850	1.19	1.13	2.9346	20073	206.4	97.252
B10	50	195	9750	50	70	3500	1.19	1.13	2.9346	20021	196.73	101.77
B11	55	173	9515	45	111	4995	1.189	1.195	1.5507	17261	124.78	138.33
B12	45	173	7785	55	111	6105	1.189	1.195	1.5507	17252	130.29	132.41
B13	50	173	8650	50	111	5550	1.189	1.195	1.5507	17257	127.54	135.31
B14	55	195	10725	45	111	4995	1.19	1.195	1.7494	19463	133.72	145.55
B15	45	195	8775	55	111	6105	1.19	1.195	1.7494	19455	141.22	137.77
B16	50	195	9750	50	111	5550	1.19	1.195	1.7494	19459	137.47	141.55

Table 4

Table 4: batches of MSN S100 and L100 in combination with PEO 303 and L100-55

Batch	B05	B06	B07	B08	B09	B10	B11	B12	B13	B14	B15	B17
MSN	95	95	95	95	95	95	95	95	95	95	95	95
S100	55	45	50	--	--	--	55	45	50	--	--	--
L100	--	--	--	55	45	50	--	--	--	55	45	50
PEO 303	45	55	50	45	55	50	--	--	--	--	--	--
L100-55	--	--	--	--	--	--	45	55	50	45	55	50
Total	195	195	195	195	195	195	195	195	195	195	195	195

All the quantities are expressed in mg

Table 5

Table 5 (a): Korsemeyer-peppas model fitting of dissolution data from B07 and B10

Model	0.1N HCL		pH 6.8	
	r2	N	r2	N
B07	0.9985	0.050	0.9987	0.59
B10	0.9981	0.49	0.9980	0.66

Table 5 (b): Simulated model for release profile of batch B13 and B16

Model	B13		B16	
	Equation	r	Equation	r
Zero-order	Q = 3.7978t + 2.2032	0.9671	Q = 4.4676t + 3.7428	0.9323
First-Order	Ln(1-Q) = -0.0369t + 2.0485	0.9830	Ln(1-Q) = -0.0701t + 0.1356	0.9702
Hixon-Crowell	(1-Q)1/3 = 0.0974t-0.07	0.9915	(1-Q)1/3 = 0.1472t-0.1533	0.9945
Higuchi	Q = 18.932t1/2 – 12.553	0.9214	Q = 22.694t1/2 – 14.598	0.9224
Korsemeyer-Peppas	lnQ = 62.348 lnt - 10.519	0.9207	lnQ = 75.763 lnt – 12.847	0.9470